Osteoblastic Bone Flare on F18-FDG PET in Non-small Cell Lung Cancer (NSCLC) Patients Receiving Bevacizumab in Addition to Standard Chemotherapy

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Abstract: Positron emission tomography (PET) is used routinely to follow therapeutic response in patients treated for non-small cell lung cancer (NSCLC). In responding patients it is generally expected that the observed decrease in fluorodeoxyglucose uptake should be similar in all lesions. In other disease entities though, isolated cases have been documented of asynchronous increases in activity in metastatic bone lesions ("bone flare") despite evidence of therapeutic response or stability in other lesions. Here, we describe four NSCLC cases in which the results of interim PET scans were misleading due to osteoblastic flare phenomenon. In all four cases, patients were treated with bevacizumab in addition to standard chemotherapy. All four patients developed isolated worsening of their skeletal metastases on PET/CT (computed tomography) analysis (increase in fluorodeoxyglucose activity) despite apparent response or stable disease elsewhere. Subsequent scans confirmed that the "worsening" was transient, consistent with a flare response. Awareness of the phenomena is important for physicians treating NSCLC patients, particularly with bevacizumab.

Key Words: Non-small cell lung cancer, Bone metastases, Bevacizumab, Chemotherapy, Bone flare, Osteoblastic flare, Osteoblastic bone reaction, Positron emission tomography, Discrepancy.

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Metastatic bone disease occurs in 30 to 40% of patients with non-small cell lung cancer (NSCLC).[1] In the initial detection of skeletal involvement, whole body fluorodeoxyglucose-positron emission tomography (F18-FDG-PET) has largely replaced bone scan due to superior specificity and concurrent tomographic images.[1] In various studies the sensitivity and specificity of PET in detecting untreated bone metastasis is estimated to be 85 and 99%, respectively.[2] There are, however, no guidelines for assessment of response in metastatic bone lesions. In clinical practice, responding bone lesions from a NSCLC primary are expected to lose intensity of FDG uptake in a manner similar to that of visceral metastases and the primary tumor. However, a paradoxical flare phenomenon with increase in bone lesion activity despite overall response has been described in several other solid tumors (breast, prostate, small cell lung cancer).[3–5] This phenomenon represents rapid bone repair around the responding lesion (increased osteoblastic activity) and may be predictive of successful systemic therapy.[6] It has been reported that up to 75% of patients with breast cancer with responding bony metastases show increased activity or new lesions due to bone repairs, with a subsequent decrease in activity 6 months later.[6] Despite the prevalence of this phenomena in breast cancer, only a few cases of bone flare have been reported in NSCLC patients on chemotherapy, and all used bone scan imaging.[7] Misinterpretation of bone flare can lead to premature cessation of successful therapy.

We present four NSCLC patients who developed discrepant increases in FDG activity in bone lesions with otherwise stable or responding disease elsewhere. Skeletal changes on imaging were indistinguishable from those seen in progressive disease, and were read as progressive disease at the time of the initial imaging report. All of these patients were treated with bevacizumab in addition to standard chemotherapy.

Case 1

A 49-year-old woman with a 3.5 cm left lower lobe primary adenocarcinoma and diffuse pulmonary and skeletal metastasis was treated with a platinum doublet and bevacizumab on a clinical trial. Her first follow-up PET/CT (computed tomography) after 2 cycles (6 weeks) showed stable size and decreased FDG uptake in her lung masses, but increased uptake in the bone lesions. Concern was raised for progression in the bones, but given her response elsewhere she was kept on the same therapy. The next PET/CT after two additional cycles revealed stability in all lung lesions, but an even more intense uptake in the previously seen skeletal lesions. Based on the concern of progression in the bones, the patient chose to discontinue all therapy. After 4 months off any conventional cancer therapy, another PET/CT documented interval progression in the primary mass, multiple

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new pulmonary and bone lesions but was read as "dramatic interval therapeutic response" in the old skeletal lesions. Thus at the time of progression, the old bony lesions looked improved by PET, when they were actually worsening along with the disease elsewhere. This result was consistent with an earlier response rather than progression in bony metastases during initial treatment with chemotherapy and bevacizumab. Misinterpretation of the results had lead to premature discontinuation of her therapy Figure 1.

Case II

A 71-year-old man with a 4.5 cm right lower lobe adenocarcinoma, lung metastases and multiple bony metastases including vertebrae was treated on a clinical trial of a platinum doublet and bevacizumab and a follow up PET/CT after 2 cycles (6 weeks) showed partial response in all lung masses and a rib that had received radiation, but increased tracer uptake in the spinal lesions. After two more cycles of therapy, the PET/CT demonstrated further decrease in FDG uptake in the parenchymal lesions, and now significantly reduced uptake in the spinal metastases as well. This confirmed flare as the most likely etiology of the previous noted increase in activity in that region.

Case III

A 51-year-old man with a 2.7 cm adenocarcinoma in the left lower lobe, hilar lymphadenopathy, and multiple hepatic lesions had multifocal metastatic bone disease as visualized on both a bone scan, and a PET scan. Therapy with carboplatin, paclitaxel, bevacizumab, and pamidronate led to dramatic improvement in his bone pain. However, imaging after 3 cycles (9 weeks) revealed a mixed lytic and blastic lesion involving the right scapula and glenoid process that had increased in size per plain film and increased density and size of other lesions on bone scan (but no new lesions). A PET/CT showed decrease in FDG uptake in the lung and liver masses but increased activity in all previously known bone metastases. After a 2 week delay in therapy based on concern for progression, he proceeded with three additional cycles of chemotherapy and bevacizumab and his next PET showed decrease in uptake in both skeletal as well as lung parenchymal lesions, consistent with earlier bone flare.

Case IV

A 47-year-old woman with a 2 cm left lower lobe adenocarcinoma, multiple small lung nodules, and numerous bone lesions had resolution of her bone pain after only one cycle of pemetrexed and bevacizumab on a clinical trial. A PET scan after 2 cycles of therapy (6 weeks) demonstrated minimal regression. After four cycles a PET scan showed stable pulmonary disease, but some increase in standard uptake value activity of her bone lesions without corresponding worsening on the CT portion and no return of her bone pain. On repeat imaging after two more cycles her tumor size was stable, but FDG uptake of the bone lesions increased further. Possible progression was considered, but the patient continued on therapy and after two additional cycles her subsequent PET scan demon-

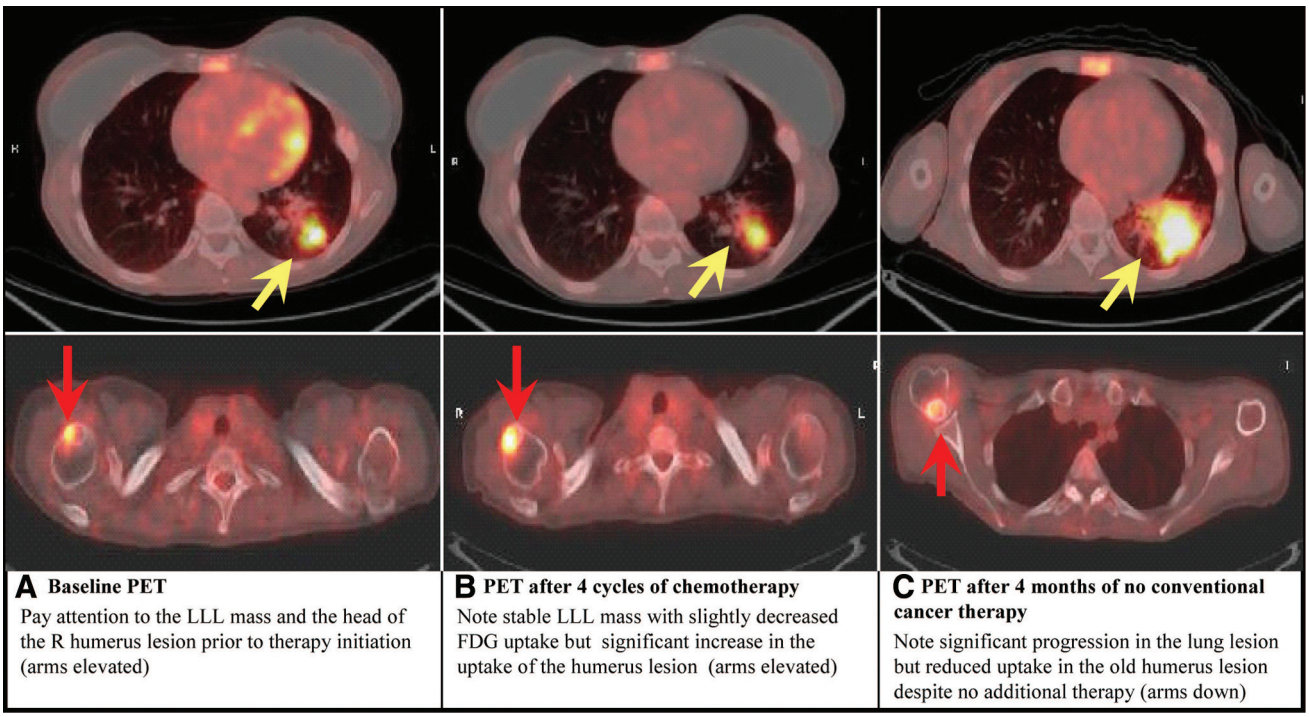

FIGURE 1. *Patient* #1, Fusion Image of changes in positron emission tomography/computed tomography (PET/CT) during therapy and after therapy cessation focusing on a lung lesion and a lesion in the right humerus. The arms are up on the first two scans and down on the last one, explaining the positional change of the humerus lesion.

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strated stability in pulmonary disease and lymph nodes and reduction of standard uptake value activity in all of the previously seen skeletal lesions.

DISCUSSION

Over a period of several months we observed four NSCLC patients with evidence of isolated increase in FDG avidity in metastatic bone lesions despite systemic response to ongoing therapy with chemotherapy and bevacizumab. In three of the patients, subsequent imaging demonstrated decrease in bone activity with ongoing systemic response, confirming flare as the etiology. One patient who stopped chemotherapy and bevacizumab treatment had "improvement" in her bone lesions when all other sites of disease progressed off treatment, also consistent with an earlier flare response.

Our experience suggests that bone flare on PET scans after several cycles of treatment for NSCLC, particularly with bevacizumab is more common than can be judged from the literature. It may be that this phenomenon is now being seen in NSCLC because of the higher response rates seen with bevacizumab combination regimens. It will be interesting to evaluate whether in NSCLC there is any correlation between the development of active bone remodeling, as evidenced by FDG flare, and improvement in overall survival as has been reported in breast cancer patients.[6]

With the development of more effective lung cancer therapies and widespread use of PET imaging in the follow up of disease response, the "bone flare" phenomenon previously described predominantly in breast cancer is now an issue in NSCLC as well. Practicing oncologists and radiologists need to be aware of the possibility of this phenomenon and exercise caution in interpretation of isolated increased FDG activity in the bone in the setting of otherwise stable or responding disease. This is particularly true in patients receiving combination regimens with higher response rates.

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